**Citation:**

Forrester MB, Merz RD. Rates of selected birth defects in relation to folic acid fortification, Hawaii, 1986-2002. *Hawaii Med J.* 2005 Dec; 64 (12): 300, 302-305.

**PubMed ID:** 16438020

**Study Design:**

Trend study

**Class:**

D - Click here for explanation of classification scheme.

**Research Design and Implementation Rating:**

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

**Research Purpose:**

To examine the potential impact of folic acid fortification on the rates of selected birth defects using data from a population-based birth defects registry in Hawaii.

**Inclusion Criteria:**

- Infants and fetuses of any pregnancy outcome (live birth, fetal death, elective termination) or any gestation age where the pregnancy ended in Hawaii, and one or more reportable birth defects were identified between conception and one year after delivery
- Cases were all infants or fetuses with one or more neural tube defects (NTDs) of 19 selected birth defects categories delivered during 1986 to 1996 or 1999 to 2002.

**Exclusion Criteria:**

- Any live-born infant, any fetuses prenatally diagnosed and electively terminated and fetuses spontaneously aborted before 1986 or after 2002
- Instances where the diagnosis was listed as "possible" or "probable."

**Description of Study Protocol:**

**Recruitment**

- All pregnancy outcomes where the pregnancy ended in Hawaii
- Data were collected or compiled from the Hawaii Birth Defects Program (HBDP)
- All live births, fetal deaths and elective terminations were included.

**Design**

- Trend study
- The study assessed whether the trend in NTD prevalence in the pre-fortification period (1986 to 1996) continued into the post-fortification period (1999 to 2002) by using data compiled from the Hawaii Birth Defects Program (HBDP), an active statewide population-based birth defects registry.

**Intervention**

1998 US-implemented compulsory folic acid fortification in cereal grain products.

**Statistical Analysis**

- Rates for each birth defect were calculated for each time period using denominators derived from birth certificates
- Rates during mandatory fortification were then compared to the corresponding pre-fortification rate by calculating rate ratios and 95 percent confidence intervals (95% CI) using Poisson probabilities
- Two trends were examined:
    - The first set was 1986 to 1996 (pre-fortification) 1999 to 2002 (mandatory fortification). This set of time periods is longer than those reported in other studies and thus less likely to be subject to wide variations in rates during one or several years
    - The second set was 1993 to 1996 (pre-fortification) 1999 to 2002 (mandatory fortification), thus using equal lengths of time both before and after fortification
- No adjustments were made for fetal deaths and elective terminations should the pregnancies have gone to term or for demographic composition of the population between the time periods.

**Data Collection Summary:**

- *Timing of measurements:* Data collected for each subject at one time point (from the Hawaii Birth Defects Program and active statewide population-based birth defects registry)
- *Dependent variables:* NTDs in infants or fetuses
- *Independent variables:* Folic acid fortification.

**Description of Actual Data Sample:**

- *Initial N:*
    - For Trend 1: 1986 to 1996 vs. 1999 to 2002, N=281,621
    - For Trend 2: 1993 to 1996 vs. 1999 to 2002, N=145,632
- *Attrition (final N):* No attrition, data collected at one time point per subject
- *Age:* Infant or fetus through age one
- *Location:* Hawaii.

**Summary of Results:**

**Table 1. Rates Per 10,000 Births of Selected Birth Defects in Hawaii Before and After Folic Acid Fortification, 1986 to 2002**

| Defect | 1986 to 1996 (212,258 Births) | | 1999 to 2002 (69,363 Births) | | | |
|---|---|---|---|---|---|---|
| | No. | Rate | No. | Rate | Ratio[1] | 95% CI[2] |
| **Neural Tube Defects** | 187 | 8.81 | 48 | 6.92 | 0.92 | 0.56 to 1.08 |
| Anencephaly | 82 | 3.86 | 22 | 3.17 | 0.82 | 0.49 to 1.33 |
| Spina bifida | 105 | 4.95 | 26 | 3.75 | 0.76 | 0.47 to 1.17 |
| **Anotia/microtia** | 73 | 3.44 | 30 | 4.33 | 1.26 | 0.79 to 1.95 |
| **Conotruncal heart defects** | 188 | 8.86 | 52 | 7.50 | 0.85 | 0.61 to 1.16 |
| Truncus arteriosus | 17 | 0.80 | 0 | 0.00 | 0.00 | 0.00 to 0.74 |
| Transposition of great arteries | 85 | 4.00 | 34 | 4.90 | 1.22 | 0.80 to 1.84 |
| Tetralogy of Fallot | 93 | 4.38 | 20 | 2.88 | 0.66 | 0.38 to 1.08 |
| **Ventricular septal defect** | 911 | 42.92 | 262 | 37.77 | 0.88 | 0.76 to 1.01 |
| **Atrial septal defect** | 426 | 20.07 | 174 | 25.09 | 1.25 | 1.04 to 1.49 |
| **Coarctation of aorta** | 57 | 2.69 | 10 | 1.44 | 1.54 | 0.24 to 1.06 |
| **Oral clefts** | 443 | 20.87 | 110 | 15.86 | 0.76 | 0.61 to 0.94 |
| Cleft palate alone | 160 | 7.54 | 37 | 5.33 | 0.71 | 0.48 to 1.02 |
| Cleft lip with or without cleft palate | 283 | 13.33 | 73 | 10.52 | 0.79 | 0.60 to 1.02 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Pyloric stenosis** | 196 | 9.23 | 41 | 5.91 | 0.64 | 0.45 to 0.90 |
| **Imperforate anus** | 115 | 5.42 | 34 | 4.90 | 0.90 | 0.60 to 1.34 |
| **Limb reduction deformity** | 99 | 4.66 | 24 | 3.46 | 0.74 | 0.45 to 1.17 |
| **Omphalocele** | 61 | 2.87 | 14 | 2.02 | 0.70 | 0.36 to 1.27 |
| **Trisomy 21** | 337 | 15.88 | 85 | 12.25 | 0.77 | 0.60 to 0.98 |

[1]Ratio of rate during 1999 to 2002 to rate during 1986 to 1996.

[2]95% CI, any cases with 1+ birth defect are included in all relevant categories.

**Table 2. Rates Per 10,000 Births of Selected Birth Defects in Hawaii Before and After Folic Acid Fortification, 1993 to 2002**

| Defect | 1993 to 1996 (76,269 births) | | 1999 to 2002 (69,363 births) | | | |
|---|---|---|---|---|---|---|
| | No. | Rate | No. | Rate | Ratio[1] | 95% CI[2] |
| **Neural Tube Defects** | 82 | 10.75 | 48 | 6.92 | 0.64 | 0.44 to 0.93 |
| Anencephaly | 33 | 4.33 | 22 | 3.17 | 0.73 | 0.41 to 0.93 |
| Spina bifida | 49 | 6.42 | 26 | 3.75 | 0.58 | 0.35 to 0.96 |
| **Anotia/microtia** | 18 | 2.36 | 30 | 4.33 | 1.83 | 0.99 to 3/49 |
| **Conotruncal heart defects** | 67 | 8.78 | 52 | 7.50 | 0.85 | 0.58 to 1.24 |
| Truncus arteriosus | 5 | 0.66 | 0 | 0.00 | 0.00 | 0.00 to 1.20 |
| Transposition of great arteries | 35 | 4.59 | 34 | 4.90 | 1.07 | 0.65 to 1.76 |
| Tetralogy of Fallot | 28 | 3.67 | 20 | 2.88 | 0.79 | 0.42 to 1.45 |
| **Ventricular septal defect** | 316 | 41.43 | 262 | 37.77 | 0.91 | 0.77 to 1.08 |
| **Atrial septal defect** | 130 | 17.04 | 174 | 25.09 | 1.47 | 1.17 to 1.86 |
| **Coarctation of aorta** | 18 | 2.36 | 10 | 1.44 | 0.61 | 0.25 to 1.40 |
| **Oral clefts** | 158 | 20.72 | 110 | 15.86 | 0.77 | 0.60 to 0.98 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cleft palate alone | 59 | 7.74 | 37 | 5.33 | 0.69 | 0.44 to 1.06 |
| Cleft lip with or without cleft palate | 99 | 12.98 | 73 | 10.52 | 0.81 | 0.59 to 1.11 |
| **Pyloric stenosis** | 71 | 9.31 | 41 | 5.91 | 0.63 | 0.42 to 0.95 |
| **Imperforate anus** | 42 | 5.51 | 34 | 4.90 | 0.89 | 0.55 to 1.43 |
| **Limb reduction deformity** | 31 | 4.06 | 24 | 3.46 | 0.85 | 0.48 to 1.50 |
| **Omphalocele** | 26 | 3.41 | 14 | 2.02 | 0.59 | 0.29 to 1.18 |
| **Trisomy 21** | 116 | 15.21 | 85 | 12.25 | 0.81 | 0.60 to 1.08 |

[1]Ratio of rate during 1999 to 2002 to rate during 1993 to 1996.

[2]95% CI, any cases with 1+ birth defect are included in all relevant categories.

**Table 3. Rates Per 10,000 Births of Selected Birth Defects in Hawaii During Various Time Periods**

| Birth Defect | 1986 to 1992 | 1993 to 1996 | 1999 to 2002 |
|---|---|---|---|
| **Neural Tube Defects** | 7.72 | 10.75 | 6.92 |
| Anencephaly | 3.60 | 4.33 | 3.17 |
| Spina bifida | 4.12 | 6.42 | 3.75 |
| **Anotia/microtia** | 4.04 | 2.36 | 4.33 |
| **Conotruncal heart defects** | 8.90 | 8.78 | 7.50 |
| Truncus arteriosus | 0.88 | 0.66 | 0.00 |
| Transposition of great arteries | 3.68 | 4.59 | 4.90 |
| Tetralogy of Fallot | 4.78 | 3.67 | 2.88 |
| **Ventricular septal defect** | 43.75 | 41.43 | 37.44 |
| **Atrial septal defect** | 21.77 | 17.04 | 25.09 |
| **Coarctation of aorta** | 2.87 | 2.36 | 1.44 |
| **Oral clefts** | 20.96 | 20.72 | 15.86 |
| Cleft palate alone | 7.43 | 7.74 | 5.33 |
| Cleft lip with or without cleft palate | 13.53 | 12.98 | 10.52 |
| **Pyloric stenosis** | 9.19 | 9.31 | 5.91 |
| **Imperforate anus** | 5.37 | 5.51 | 4.90 |
| **Limb reduction deformity** | 5.00 | 4.06 | 3.46 |
| **Omphalocele** | 2.57 | 3.41 | 2.02 |

| | | | |
|---|---|---|---|
| **Trisomy 21** | 16.25 | 15.21 | 12.25 |

Any cases with 1+ birth defect are included in relevant categories.

**Author Conclusion:**

The findings of this study would tend to support the supposition that fortification of enriched cereal grains have reduced the rates of NTDs and other birth defects in Hawaii.

***Reviewer Comments:***

- *No discussion of statistical significance for differences between rates or if reduction in rates is statistically significant. The relatively small number of cases limits the statistical significance of the analysis*
- *Information on folic acid supplementation is not reported*
- *Study did not look at or control for demographics. The authors did not control for temporal changes in demographic factors such as race or ethnicity or maternal age distribution.*

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***Research Design and Implementation Criteria Checklist: Primary Research***

**Relevance Questions**

| | | |
|---|---|---|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | N/A |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | N/A |

**Validity Questions**

| | | |
|---|---|---|
| **1.** | **Was the research question clearly stated?** | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |

| | | |
|---|---|---|
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |
| 1.3. | Were the target population and setting specified? | Yes |
| **2.** | **Was the selection of study subjects/patients free from bias?** | Yes |
| 2.1. | Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study? | Yes |
| 2.2. | Were criteria applied equally to all study groups? | Yes |
| 2.3. | Were health, demographics, and other characteristics of subjects described? | No |
| 2.4. | Were the subjects/patients a representative sample of the relevant population? | Yes |
| **3.** | **Were study groups comparable?** | ??? |
| 3.1. | Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT) | N/A |
| 3.2. | Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline? | N/A |
| 3.3. | Were concurrent controls used? (Concurrent preferred over historical controls.) | N/A |
| 3.4. | If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis? | ??? |
| 3.5. | If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.) | ??? |
| 3.6. | If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")? | N/A |
| **4.** | **Was method of handling withdrawals described?** | Yes |
| 4.1. | Were follow-up methods described and the same for all groups? | N/A |
| 4.2. | Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.) | N/A |
| 4.3. | Were all enrolled subjects/patients (in the original sample) accounted for? | Yes |
| 4.4. | Were reasons for withdrawals similar across groups? | N/A |

| | | |
|---|---|---|
| 4.5. | If diagnostic test, was decision to perform reference test not dependent on results of test under study? | N/A |
| **5.** | **Was blinding used to prevent introduction of bias?** | Yes |
| 5.1. | In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate? | N/A |
| 5.2. | Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.) | Yes |
| 5.3. | In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded? | Yes |
| 5.4. | In case control study, was case definition explicit and case ascertainment not influenced by exposure status? | N/A |
| 5.5. | In diagnostic study, were test results blinded to patient history and other test results? | N/A |
| **6.** | **Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?** | Yes |
| 6.1. | In RCT or other intervention trial, were protocols described for all regimens studied? | N/A |
| 6.2. | In observational study, were interventions, study settings, and clinicians/provider described? | Yes |
| 6.3. | Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect? | Yes |
| 6.4. | Was the amount of exposure and, if relevant, subject/patient compliance measured? | N/A |
| 6.5. | Were co-interventions (e.g., ancillary treatments, other therapies) described? | N/A |
| 6.6. | Were extra or unplanned treatments described? | N/A |
| 6.7. | Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups? | N/A |
| 6.8. | In diagnostic study, were details of test administration and replication sufficient? | N/A |
| **7.** | **Were outcomes clearly defined and the measurements valid and reliable?** | Yes |
| 7.1. | Were primary and secondary endpoints described and relevant to the question? | Yes |
| 7.2. | Were nutrition measures appropriate to question and outcomes of concern? | N/A |
| 7.3. | Was the period of follow-up long enough for important outcome(s) to occur? | Yes |
| 7.4. | Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures? | Yes |

| | | |
|---|---|---|
| 7.5. | Was the measurement of effect at an appropriate level of precision? | Yes |
| 7.6. | Were other factors accounted for (measured) that could affect outcomes? | No |
| 7.7. | Were the measurements conducted consistently across groups? | Yes |
| **8.** | **Was the statistical analysis appropriate for the study design and type of outcome indicators?** | Yes |
| 8.1. | Were statistical analyses adequately described and the results reported appropriately? | Yes |
| 8.2. | Were correct statistical tests used and assumptions of test not violated? | Yes |
| 8.3. | Were statistics reported with levels of significance and/or confidence intervals? | Yes |
| 8.4. | Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? | N/A |
| 8.5. | Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? | No |
| 8.6. | Was clinical significance as well as statistical significance reported? | No |
| 8.7. | If negative findings, was a power calculation reported to address type 2 error? | No |
| **9.** | **Are conclusions supported by results with biases and limitations taken into consideration?** | Yes |
| 9.1. | Is there a discussion of findings? | Yes |
| 9.2. | Are biases and study limitations identified and discussed? | Yes |
| **10.** | **Is bias due to study's funding or sponsorship unlikely?** | Yes |
| 10.1. | Were sources of funding and investigators' affiliations described? | Yes |
| 10.2. | Was the study free from apparent conflict of interest? | Yes |